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(54) Title: INHIBITION OF THE FORMATION OF NITROSAMINES (57) Abstract Reaction of amine-containing substrates with hydrogen peroxide can suffer from certain problems, especially in the presence of transition metals. These problems include both in situ generation of impurities and particularly nitrosamines, which are allegedly carcinogenic, and also impaired product formation. The problems can be ameliorated by employing in the reaction mixture free radical scavengers, including in particular phenols and polyhydroxy-substituted aromatic compounds. The scavengers are advantageously employed in conjunction with a metal chelating agent such as polycarboxylic acid or an organopolyphosphonic acid.		

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Inhibition of the Formation of Nitrosamines

The present invention relates to a process for the inhibition of the formation of nitrosamines during the reaction of a compound containing an amine functionality, and in particular from secondary or tertiary amines.

Background to the present invention

Compounds containing an amino functionality can be oxidized with hydrogen peroxide, sometimes with an additive such as a catalyst in order to promote the reaction or sometimes in the absence of a catalyst, depending on the inherent reactivity of the substrate. Many papers or patents describe variations to the reaction between amines and hydrogen peroxide. For example, US Patent Specification no 4 247 480 to Nissan Chem Ind KK suggests the addition of a chelating agent selected from EDTA or stannate together with carbonic acid or a carbonate.

Disadvantageously, however, there is a tendency for nitrosamines to be formed as byproducts in reaction mixtures which contain amines, particularly secondary or tertiary amines and hydrogen peroxide. This is inevitably the case during reaction between those two reactants but it can also occur if such an amine is itself a reaction product or intermediate. For example, when tertiary amines are being converted to amine oxides by reaction with hydrogen peroxide, there is a distinct tendency for nitrosamines to be produced as a byproduct. The formation of nitrosamines is disadvantageous for several reasons, of which the most significant identified to date is the fact that many nitrosamines are carcinogenic. At least some of the nitrosamines are quite volatile, so that either in the course of the reaction or subsequently during storage or use of the main product, such volatile nitrosamines can be released into the atmosphere and thus can be inhaled by persons in the vicinity. They can be absorbed through the skin by dermal contact. This can be particularly significant

for some amino derivatives such as amine oxides, in that one of their major uses is in personal hygiene products, such as shampoos or cleansing lotions which are skin contact products. Consequently, it is highly desirable
5 to find ways of inhibiting the formation of such carcinogenic byproducts to preserve the health of chemical process operators and any subsequent user of the products.

As a second disadvantage, though of rather less
10 importance, a number of the byproduct nitrosamines are brightly colored, such that their presence, even in low amounts, tends to impart that color to the main product. If as is the case with amine oxides, the product would otherwise be white, then the presence of the byproduct
15 can render the product less desirable commercially, by failing to meet color specifications.

It has been observed that the peroxide/amine reaction can be sensitive to the presence of a number of interfering substances including metals which can promote
20 by-reactions. Such substances can be present as impurities in the reactants, possibly as a result of the method of their manufacture, or introduced in water added as diluent in the reaction mixture, or can be extracted from the pipework or walls of the reaction vessels or
25 holding tanks or can result from inadvertant ingress of foreign bodies such as dust. The concentration of such substances correlates to a reasonable extent with the extent of nitrosamine formation. Herein, when high levels of such interfering substances are present, though
30 still within the range that can be encountered in practice, the conditions are sometimes described as "stress conditions".

In US Patent 5 023 376 (Shehad et al) and the corresponding EP-A-0 409 043 (Interox America), it has
35 already been proposed to conduct amine/hydrogen peroxide reactions in the presence of a specified selection of aminopolymethylenephosphonate compounds. Together with

other beneficial effects, it was found that their addition, in appropriate concentrations, resulted in the measurable reduction in the rate and/or extent of formation of nitrosamines. It can therefore be deduced from the data disclosed therein that at least some transition metal ions are in some way implicated in the mechanism for nitrosamine formation. The problem was ameliorated by chelation with the selected phosphonates, but either to a lesser extent or not appreciably by employing other organophosphonates outside the selection. From the foregoing, it was deduced that some further mechanism may be operating to generate nitrosamines or that there was some hitherto unidentified factor within the existing metal ion catalyzed route for nitrosamine formation that was contributing to the by-product formation.

Object of the present invention

It is an object of the present invention to find alternative or additional means to inhibit the formation of nitrosamines in reaction mixtures containing amines and hydrogen peroxide.

Brief Summary of the Invention

According to the present invention there is provided a process for the inhibition of nitrosamine formation in a reaction mixture containing hydrogen peroxide and a secondary or tertiary amine which is characterized by incorporating in the mixture an effective amount of a free radical scavenger.

According to a related aspect of the present invention, there are provided reaction mixtures containing a reactive concentration of a secondary or tertiary amine and of hydrogen peroxide in which is incorporated a free radical scavenger in a concentration that is effective to inhibit nitrosamine formation.

Herein, the term "effective" with regard to free radical concentration or amount means such an amount or concentration which causes a detectable reduction in

measurable total nitrosamine concentration in the reaction mixture. The term "inhibit" indicates at least a partial suppression of the rate or extent of nitrosamine formation.

5 Detailed description of the invention.

Free radical scavengers are well known in the field of organic synthesis and many commercial products are sold specifically for that function. In general, the scavengers are selected from amongst phenols or polyols
10 or thiols. Though not exclusively, it is generally desirable to select scavengers having a recognized capability to scavenge hydroxyl radicals.

Phenol itself may be used. Many particularly suitable scavengers are selected from phenols which satisfy the
15 general formula i):-



in which R represents at least one substituent selected
20 from alkyl, ether, hydroxyl, carboxylic acid and aliphatic carboxylic acid ester groups. Normally R in formula i) represents from 1 to 4 substituents.

The effectiveness in scavenging of phenolic compounds is presently believed to derive at least in part from the
25 proximity of the benzene nucleus to the hydroxyl group, and thereby take advantage of charge delocalization following interaction of a free radical with the scavenger. Nonetheless, the present invention is not predicated upon any theory, belief or explanation given
30 herein as to how or why the chosen materials described herein function, but instead on the results obtained.

In some phenolic scavengers according to formula i), R represents a plurality of alkyl substituents, particularly low weight groups from methyl to butyl, and
35 especially substituents ortho and/or para to the hydroxyl group. Preferably all three ortho and para positions are alkyl substituted in such scavengers, such as in 2,6-di-t-butyl-4-methylphenol.

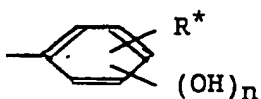
In a number of particularly suitable scavengers for use in the present invention, R represents in formula i) one or two hydroxyl substituents, and optionally at least one further non-hydroxyl substituent.

5 In scavengers according to formula i) in which R represents a plurality of substituents, each substituent may be the same or different. In several instances, R represents an alkyl, carboxylic acid/ester or ether substituent in addition to representing at least one
10 hydroxyl group.

One suitable sub-class of phenolic scavengers comprises polyhydroxybenzoic acid or alkyl ester derivatives thereof, the benzene nucleus optionally being further substituted by one or more alkyl substituents. Normally
15 not more than a single carboxylic acid/ester substituent is present. Included within that sub-class are the dihydroxybenzoic acids, gallic acid, pyrogalllic acid and ester derivatives thereof. Other suitable sub-classes
20 comprise polyhydroxyalkylbenzenes or ether derivatives thereof. Representatives of that subgroup include alkylresorcinols and alkylhydroquinones.

Where R comprises or includes an alkyl group, either as a substituent in its own right or as part of an ester or ether substituent, said alkyl moiety may conveniently
25 contain up to 6 carbons which can be linear or branched for propyl to hexyl, including tertiary groups for butyl to hexyl. Each of said alkyl groups, if a plurality is present, may be the same or different.

As a variation of the foregoing, some of the suitable
30 phenol compounds comprise alkanes, such as a C₃ to C₆ alkane, often linear, which are substituted by a hydroxyphenyl substituent. In such scavengers, a plurality of hydroxyphenyl substituents such as up to 4 may be present. Such hydroxyphenyl substituents often
35 obey formula ii):-



- in which R* represents hydrogen or at least one alkyl group which may be selected from the same range of alkyl groups as for R in general formula i) and n represents an integer of from 1 to 3. In compounds obeying formula ii), R* can desirably represent two alkyl groups, such as one being a methyl and the other a butyl (particularly t-butyl). Desirably, the or one of the hydroxyl substituents is at the 4 position around the nucleus, as for example in a 2,5-dialkyl-4-hydroxyphenyl substituent.
- 10 The scavenger can also be selected from thiols or disulfides. Representative thiols embrace thiocarboxylic acids, including in particular low molecular weight compounds containing one or two aliphatic carboxylic acid substituents, each such
- 15 substituent containing up to about eight carbons. Some preferred compounds comprise thiodialiphatic carboxylic acids, such as thiodibutanoic acid. In such compounds the two aliphatic acids are often, though not exclusively, the same, as for example in thiodipropionic
- 20 acid or thiodiacetic acid. Other thiols include aromatic or heterocyclic thiols, such as 2-benzimidazole-thiol and related compounds. Disulfides include alkylthiuram disulfides and bis(dimethylthiocarbamoyl)-disulfide.
- 25 It will also be understood that a mixture of any two or more of the foregoing scavengers can be employed, including explicitly a mixture of examples from any two or more sub-classes of scavenger. Particular combinations comprise an alkylated hydroxyanisole with an
- 30 alkyl gallate or an alkylcresol, including specifically 2-t-butyl-4-hydroxyanisole with either propyl gallate or 2,6-di-t-butyl-p-cresol.

Secondary or tertiary aliphatic alcohols have also been found in some instances to ameliorate the extent and/or

35 rate of nitrosamines formation and it is convenient to employ such alcohols for example those containing at least 3 and particularly from 4 to 6 carbons. In one

advantageous method of employment, such alcohols can act as solvent for phenolic scavengers, some of which are only poorly soluble in some reaction media, thereby enabling the latter to be more readily dispersed through the reaction medium or in at least one of the reactants, such as into the hydrogen peroxide.

The concentration of scavenger to employ in the reaction mixture in practice depends upon its inherent capability to scavenge and the anticipated level at which free radicals will be generated therein. The latter, in turn, is believed to depend, amongst other factors, on the extent of contamination and the nature of the contaminants, including a wide range of metal ions. A number of transition metal ions can induce free radical formation by interaction with hydrogen peroxide, ie with the co-reagent. Other free-radicals can arise from interaction of radiation with hydrogen peroxide or other constituents of the reaction mixture.

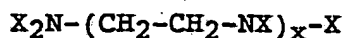
In practice, it is convenient to relate the amount of scavenger to add to the amount of amine in the reaction mixture. It is desirable to employ a mole ratio at least 10^{-5} mole of scavenger per mole of amine and in many instances a mole ratio of at least 10^{-4} :1. The upper limit is at the discretion of the user and takes into account the expected maximum contaminant incursion. The mole ratio is normally not greater than 10^{-1} mole of scavenger per mole of amine and in many instances, the benefit is attained using scavenger:amine mole ratio of not more than about 10^{-2} :1.

It will be understood that the scavenger may be introduced directly into the reaction mixture or at least a part of it may be introduced via one or both of the two reagents, namely the amine or the hydrogen peroxide solutions. Naturally, if it is introduced via either of the reagent solutions, the concentrations of scavenger therein are usually calculated so as to enable the total amount to fall within the above-identified limits in the

reaction mixture. If desired, all the scavenger can be present when the amine and hydrogen peroxide reactants are mixed together, or a fraction, such as up to about half, of the scavenger may, if preferred, be introduced during the course of the reaction.

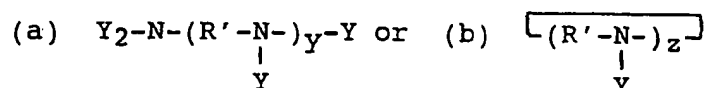
In a number of reactions the hydrogen peroxide is employed in a small molar excess to the amine. In such circumstances, the desired concentration of scavenger can be obtained by dissolving it at approximately the same mole ratio relative to the hydrogen peroxide as would be desired relative to the amine. Naturally, the feasibility of supplying the entire amount of scavenger in the hydrogen peroxide solution is dependent upon the solubility of the former in the latter. In the case of aliphatic alcohols, this is readily achieved without any significant constraint, but for certain of the higher molecular weight aromatic compounds their solubility constrains the maximum that can be introduced this way. For such less soluble scavengers, it is preferable for at least a proportion of the total amount to be added either separately into the reaction mixture or into the amine reactant solution.

Preferably, the scavenger is employed in conjunction with a metal chelant such as a polyaminocarboxylic acid or organic polyphosphonic acid or a salt thereof. Many of the polyaminocarboxylic acids can be represented by the general formula



in which X represents $-CH_2CO_2H$ or a salt thereof and x an integer from 0 to 2, including EDTA and DTPA.

Organic phosphonates which can be employed together with the scavengers include hydroxyalkylenephosphonic acids, such as hydroxyethylene-1,1-diphosphonic acid and polyaminomethylene phosphonic acids. A number of such organic phosphonates are selected from alkylene aminomethylenephosphonic acids or water soluble salts thereof obeying either of the general formulae:-



in which Y represents a group of formula $-\text{CH}_2-\text{PO}_3\text{M}_2$ in
 5 which M represents H or a non-transition metal cation
 conferring water-solubility, R' represents an aliphatic
 diradical of 2 to 6 carbons, preferably 2 or 3 carbon
 atoms length or an alicyclic diradical containing from 2
 to 6 carbon atoms, y represents an integer selected from
 10 0 to 4, preferably from 1 to 4 and z represents an
 integer selected from 4 to 6. By the choice of
 particularly preferred metal chelates in conjunction with
 the scavenger, it is possible to combine the beneficial
 effects of the scavenger on inhibiting the formation of
 15 nitrosamines with the beneficial effect on inhibiting
 nitrosamine formation and improving product yield
 obtainable from the selected chelates. The two
 components complement each other.

Within the range of organic phosphonic acid compounds
 20 encompassed within formula 1 in the process of the
 instant invention, n is particularly suitably 1 or 2 and
 in compounds according to formula 2, m is preferably 4 or
 6. For both formulae, adjacent amino groups are
 preferably separated by two linear carbon atoms which may
 25 bear simply hydrogen atoms or be substituted by a methyl
 group or form part of a 6 or 5 membered carbocyclic ring.
 It will be recognized that in such compounds, the length
 of the diradical is two carbon atoms. M can often
 represent a hydrogen atom or an alkali metal, ammonium or
 30 magnesium ion. Within formula 1, particularly preferred
 compounds include ethylenediaminetetrakis
 (methylenephosphonic acid), diethylenetriaminepentakis
 (methylenephosphonic acid) and 1,2-cyclohexane-
 diaminetetrakis(methylenephosphonic acid) and the
 35 corresponding fully or partly neutralized sodium,
 potassium or ammonium salts thereof. Other suitable
 aminophosphonic acid compounds are the cyclic compounds

within formula 2 which include tetracyclenetetrakis (methylenephosphonic acid) and hexacyclenehexakis (methylenephosphonic acid) and the corresponding fully or partly neutralized sodium, potassium or ammonium salts thereof.

Normally, the amount of chelate such as the selected phosphonic acid compounds is at least 10^{-5} moles per mole of amine and often from 5×10^{-5} to 10^{-3} moles per mole amine.

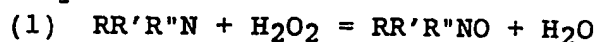
One simple basis for selecting its amount comprises the total weight of the reaction mixture. The concentration of the chelate such as the preferred phosphonic acid compounds is preferably at least 15 ppm and desirably in the range of from 50 to 500 ppm, by which we mean parts by weight per million parts of the reaction mixture. It will be recognized that as concentrations rise from 15 to 50 ppm, the likelihood increases that the level of chelate and especially of preferred phosphonic acid compounds will be able to retain reaction efficiency for the desired reaction for an increasingly large proportion of transition metal contaminations and the combination of scavenger and chelate inhibit nitrosamine formation.

It will be recognized that the chelating compounds, eg phosphonic acid compounds can be introduced into the reaction mixture as a separate component thereof, or if more convenient, they can be incorporated together with one of the other components of the reaction mixture, such as preferably the aqueous hydrogen peroxide feedstock solution. It is especially desirable to employ concentrated hydrogen peroxide solutions which have been stored for at least a few days containing the aminophosphonic acid compounds. By so doing, it is believed that the resultant interaction between the aminophosphonic acid and the hydrogen peroxide induces a beneficial change to the phosphonic acid structure, possibly involving oxidation at the nitrogen atoms.

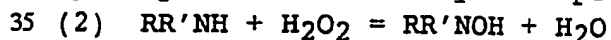
Naturally, the concentration of the phosphonic acid compounds in the hydrogen peroxide solution is selected in the light of the amount of hydrogen peroxide that it is intended to employ, and the concentration of hydrogen peroxide in the feedstock solution. Thus, to some extent, the concentration of the phosphonic acid compounds in the reaction mixture can vary depending upon the choice of amine being oxidized and its concentration in the peroxide solution can be prior adjusted to make due allowance for reagent useage to ensure that a suitable concentration of phosphonate is employed in the reaction mixture.

It will be recognized that the scavenger and chelate may be introduced together or separately into the reaction mixture. Thus, by way of example, in one embodiment, the chelate and scavenger are both premixed with the hydrogen peroxide solution, either as obtained from the supplier or in a dilution step. Alternatively, in other embodiments, all or part of the scavenger is introduced via the amine solution or directly into the reaction mixture and any chelate is introduced via the hydrogen peroxide solution.

The instant invention is particularly appropriate for use in the oxidation of substrates containing a secondary or tertiary amine group. Such reactions are often, though not exclusively conducted in aqueous conditions, ie water comprising the principal solvent, and some water is usually present either introduced with or arising in situ from the reaction of hydrogen peroxide. Particular reactions include the formation of amine oxides which obey:-

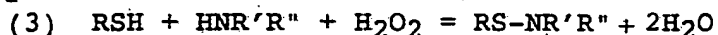


but can also be used in reactions for making hydroxylamines which may be expressed as:-

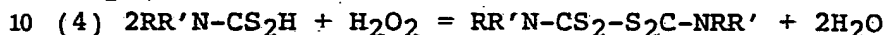


The invention is also appropriate for reactions involving a third reactant, which reactions naturally permit the

two component interaction between amine and hydrogen peroxide. One particular example thereof comprises the production of sulfenamides, the reaction being:-



5 Where the amine containing substrate also contains a further functionality which reacts in the presence of hydrogen peroxide, this too can result in nitrosamine formation as an undesirable by-product. One example comprises



The invention is applicable to any secondary or tertiary amine which can be oxidized using hydrogen peroxide. Thus, in particular it is applicable to amines in which the nitrogen substituents R, R' and R''
15 each represent the same or different alkyl groups, each containing at least 1, often from 1 to 30 carbon atoms, and at least one of the groups can be a cycloalkyl group. The two groups R and R' can combine with each other and the nitrogen atom to form a heterocyclic amine containing
20 at least 4 carbon atoms, which optionally can itself be nuclearly substituted by an oxygen atom. One or more of the alkyl groups may have an aromatic substituent, e.g. dimethylaniline. The aliphatic amine substrate can also contain an ethoxylate or propoxylate chain, containing
25 from 1 to 15 units. The aliphatic or heterocyclic amine substrate normally contains from 2 up to 50 carbon atoms. In many instances, the molecular weight of the amine substrate will fall within the range of from 80 to 325, and many of which contain from 6 to 22 carbon atoms.

30 Suitable low molecular weight amine substrates include dimethylamine and n- or isobutyldimethylamine, and the corresponding diethylamine compounds. Others include di and tributylamine, and cyclopentyl dimethylamine.

35 In a number of desirable starting materials, at least one of the substituents R, R' and R'' in the amine comprises a substituent containing at least 6 carbon

atoms such as from 8 to 18 carbons. In some of such starting materials, only one substituent of R, R' and R" contains at least 6 carbons and in other starting materials, two substituents each contain at least 6 carbons. Such a substituent can comprise a long chain alkyl or cycloalkyl group. The long chain alkyl substituent may be linear, branched, or further substituted by or otherwise include within its structure a cycloalkyl group. Particular mention is made of linear C8 to C16 alkyl groups. The cycloalkyl substituent may be substituted by a short or long chain alkyl group. The remaining substituent or substituents of R, R' and R", are often short length alkyl groups containing from 1 to 5 carbon atoms, and in many instances are conveniently methyl or ethyl substituents. Thus, in one subset of suitable amines R and optionally R' is a linear C8 to C16 alkyl group or cyclohexyl and R' and R", if present and not already described, are methyl or ethyl. Examples of such alkylamines include hexyldimethylamine, 2-ethylhexyldimethylamine, octyldimethylamine, decyl-dimethylamine, dodecyldimethylamine, tetradecyl-dimethylamine, hexadecyldimethylamine and octadecyl-dimethylamine. Other examples include decylbutylethyl-amine, hexadecylhexylmethylamine, trioctylamine, cyclohexyldimethylamine, dicyclohexylmethylamine and cyclododecyldimethylamine.

Suitable heterocyclic amines include piperidine and morpholine and alkyl N-substituted derivatives thereof, and especially those in which R" is methyl or ethyl.

The invention process preferably employs at least a stoichiometric amount of hydrogen peroxide, which is often introduced in the form of a concentrated aqueous solution. In practical applications, it is often possible to employ under non-ideal reaction conditions, ie those in which significant contamination has occurred, a similar amount of peroxide to that which has hitherto

been suggested in the art for reacting with the same substrate under "ideal" conditions. The benefit from employing free radical scavenger is manifested by inhibiting the extent of nitrosamine contamination particularly under contaminated conditions and together with the selected phosphonate compounds enabling a high substrate conversion to be maintained even under non-ideal conditions. In consequence, for example, the mole ratio of peroxide to aliphatic or heterocyclic tertiary amines in reaction (1) is normally not greater than 4:1, often less than 2:1 and in many practical instances is selected in the range of from 1.05:1 to 1.2:1. For reactions (2), (3) and (4), the amount of hydrogen peroxide to the secondary amine is normally less than ten times the stoichiometric amount and is preferably from about twice to four times the stoichiometric amount, ie the mole ratio is preferably from 2:1 to about 4:1 in reaction (2) or (3), and from 1:1 to 2:1 for reaction (4).

The invention process is normally carried out at a temperature of above ambient and often at up to about 80°C. All or most of the reactions can conveniently be effected at a temperature within the range of 40 to 75°C.

The reaction period is normally selected taking into account the reaction temperature and whether it is process (1), (2) or (3). In many instances, the period is chosen within the range of from 2 to 10 hours. The reaction period includes the period over which the hydrogen peroxide is normally introduced into the reaction mixture. This introduction period is often at least 20 minutes and normally not longer than about 100 minutes. In many instances it is from about 30 to about 60 minutes.

Having described the invention in general terms, specific embodiments thereof will hereinafter be described more fully by way of example thereof.

Comparison 1 and Examples 2 to 5

This Comparison and these Examples were each carried out using the following general method:-

Dodecyldimethylamine (0.2012 moles, 42.94g), and
5 sufficient pure water to 150g, ie approximately 106.9g, were charged into a passivated 250 mL reaction flask, at ambient temperature together with 0.16g of the stock metal solution described below to introduce 0.011 mmoles of transition metal impurities and thereby create stress
10 conditions. A chelating agent, DTPA, viz diethylene-triaminepentacarboxylic acid, 0.043 mmoles, was then introduced into the mixture to provide a mole ratio to the metal of about 4:1.

The stock metal solution was obtained by dissolving
15 CuSO₄.5H₂O, 0.393g, MnSO₄.H₂O, 0.1475g, K₂CrO₄, 0.0935g, Fe(NH₄)₂(SO₄)₂.6H₂O, 3.5106g, AlK(SO₄)₂.12H₂O, 8.791g in 500 mL water (deionized) containing 20 mL of 10%w/w sulfuric acid solution. It contained a total of 2350 ppm metals concentration. Thus, the concentration of metals
20 in the reaction mixture was about 2.3 ppm.

The reaction mixture was then heated to a temperature of 60°C and stirred. An aqueous hydrogen peroxide solution, 50% w/w solution, stabilized by sodium pyrophosphate at 70 ppm calculated as PO₄, 15.03g, was
25 then delivered into the reaction mixture at a constant slow rate during the subsequent 45 minutes. In the Examples, but not in the Comparison, the hydrogen peroxide solution also contained 2.0 mmoles of a free radical scavenger, as specified below. When all the
30 hydrogen peroxide had been introduced, the reaction temperature was increased to 75°C and the reaction permitted to continue for a total of 4 hours. The mixture was then cooled and analyzed for yield of amine oxide and for the production of by-product volatile
35 nitrosamines, specifically methyldodecyl nitrosamine (MDNA) and nitrosodimethylamine (NDMA).

The free radical scavengers were respectively 2,6-di-tert-butyl-4-methylphenol (BHT) in Ex2, butylated hydroxyanisole, a mixture of 2-tert-butylmethoxy anisole and 3-tert-butylmethoxy anisole (BHA) in Ex3, ethyl gallate (EtG) in Ex4 and propyl gallate (PrG) in Ex5.

The results for the respective nitrosamine and total nitrosamine contents of the reaction mixture are given below.

	Scavenger	Nitrosamine content (ppb)		
		MDNA	NDMA	total
10 Comparison 1	-	2430	627	3057
Example 2	BHT	1420	374	1794
Example 3	BHA	652	127	779
Example 4	EtG	334	73	407
15 Example 5	PrG	230	78	308

From the foregoing, it can be seen that the addition of a free radical scavenger to a reaction mixture which already contained a carboxylate chelating agent resulted in a marked reduction in nitrosamine formation, and especially when ethyl gallate or propyl gallate was employed.

Comparison 6 and Examples 7 to 12

The procedure of Comparison 1 and Examples 2 to 5 was repeated, but substituting cyclohexane-1,2-diaminotetramethylenephosphonic acid (CDTMPA) for the DTPA, also in the same mole ratio of 4.3:1 to the metals, and in the Examples 2.0 mmoles of the following scavengers introduced into the reaction mixture:-
BHT in Ex7, BHA in Ex8, EtG in Ex9, PrG in Ex10,
30 thiodipropionic acid (TPA) in Ex11 and 2-butanol (BuL) in Ex12.

	Scavenger	Nitrosamine content (ppb)		
		MDNA	NDMA	total
Comparison 6	-	839	669	1508
Example 7	BHT	212	123	335
5 Example 8	PHA	151	125	276
Example 9	EtG	57	30	87
Example 10	PrG	59	21	80
Example 11	TPA	444	97	541
Example 12	BuL	582	679	1261

10 From the foregoing, it can be seen that the addition of a free radical scavenger to a reaction mixture which already contained a phosphonic acid chelating agent resulted in a marked reduction in nitrosamine formation, and especially when ethyl gallate or propyl gallate was
15 employed. It can be seen that the combination of a phosphonic acid chelating agent and an hydroxybenzoic acid free radical scavenger was especially effective at inhibiting the formation of nitrosamine byproducts during the reaction.

What is claimed is:-

- 1 A process for the inhibition of nitrosamine formation in a reaction mixture containing hydrogen peroxide and a secondary or tertiary amine which is characterised by incorporating in the mixture an effective amount of a free radical scavenger.
- 2 A process according to claim 1 in which the scavengers are selected from amongst phenols or polyols, or thiols, optionally containing a further substituent.

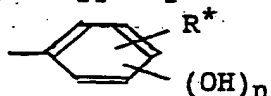
- 3 A process according to claim 2 in which the scavenger comprises a phenol which satisfies general formula i):-



in which R represents at least one substituent selected from alkyl, ether, hydroxyl, carboxylic acid and carboxylic acid ester groups.

- 4 A process according to claim 3 in which R in formula i) for the scavenger represents from 1 to 4 substituents.
- 5 A process according to claim 3 in which R in formula i) represents at least one hydroxyl substituent and optionally at least one alkyl substituent.
- 6 A process according to claim 5 in which the scavenger is an acid compound selected from dihydroxybenzoic acids, gallic acid, and pyrogalllic acid and from an ester or ether derivative of said acid compound.

- 7 A process according to claim 4 in which the scavenger comprises a C3 to C6 alkane substituted by up to 4 hydroxyphenyl substituents, which obey formula ii):-



in which R* represents at least one alkyl group containing up to 6 carbons and n represents an integer of from 1 to 3.

- 8 A process according to claim 2 in which the scavenger is a thiodicarboxylic acid containing up to eight carbons.
- 9 A process according to claim 2 in which the scavenger is employed in molar ratio to the amine of from 10^{-5} :1 to 10^{-1} :1.
- 10 A process according to claim 1 in which the scavenger is employed in conjunction with at least sufficient organic chelating agent to chelate transition metal impurities in the reaction mixture.
- 11 A process according to claim 10 in which the chelating agent is an aminopolycarboxylic acid or an organic polyphosphonic acid.
- 12 A process according to claim 11 in which the chelating agent is employed in a molar ratio to the amine of from 10^{-5} :1 to 10^{-1} :1.
- 13 A reaction mixture containing a reactive concentration of a) a secondary or tertiary amine and b) hydrogen peroxide in which there is incorporated a free radical scavenger in a concentration that is effective to inhibit nitrosamine formation.
- 14 A process for inhibiting nitrosamine formation in a reaction mixture containing hydrogen peroxide and a secondary or tertiary amine or in such a reaction mixture containing a radical scavenger and substantially as described herein with respect to any novel feature or any novel combination of features herein.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04022

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : CO7C 209/00

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/2, 564/15, 564/76, 564/102, 564/298, 564/300, 564/301, 540/474, 544/173, 546/184, 568/701, 568/716, 568/717

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS

Nitrosamine inhibition, phenols, polyols, aromatic polyols, thiols, disulfide, hydrogen peroxide, secondary and tertiary amine.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	U.S. A 5,023,376 (Shehad et al) 11 June 1991. See entire document.	1-14
Y	EP 320694 (Bauer et al) 21 June 1989 See the entire document.	1-9, 14
Y	J56083465, (NIPPON OILS & FATS KK) 08 July 1981 See the the English abstract.	1-9, 14
Y	NL 7401261 (FMC CORPORATION), 06 August 1974 See pages 13-15 and page 10.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	
A document defining the general state of the art which is not considered to be part of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
E earlier document published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O document referring to an oral disclosure, use, exhibition or other means	*Z* document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

02 AUGUST 1993

Date of mailing of the international search report

SEP 09 1993

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04022

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

564/2, 564/15, 564/76, 564/102, 564/298, 564/300, 564/301, 540/474, 544/173, 546/173, 546/184, 568/701, 568/716,
568/717